CASE REPORT

Erythroblastosis and Leukemia

A Case Report Illustrating Variations in the Clinical Picture

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Following the discovery of a striking and prolonged erythroblastosis, our interest was stimulated in this subject. The subsequent course of events in this patient was even more unusual since the erythroblastosis finally gave way to the typical picture of acute myeloblastic leukemia. This subtle transformation from what seemed to be a malignant erythroid proliferation to a still more malignant myeloid growth suggested that these events were not merely fortuitous. The presence of nucleated red cells in the blood is always an indication of some serious disturbance. Usually this is a secondary phenomenon; at times, however, as in the present case, it becomes the outstanding and central abnormality.

Before discussing the patient in whom the erythroblastosis was so prominent, it is necessary to give a short survey of the syndromes in which nucleated red cells may be found in the peripheral blood.

Historical

1. Acute “Primary” Erythroblastosis

In 1926 Di Guglielmo1 described the syndrome of acute “primary” erythroblastosis, which was characterized by an acute or subacute anemia with numerous erythroblasts. Since then similar cases have been described by others (cf. Mallarmé and Moulounguet). Occasionally, leukocytosis with immature white forms is found at the same time. Examination of the bone marrow shows an abnormal proliferation of the erythropoietic system. There is also an extensive infiltration of erythroblasts in liver, spleen and lymph glands and although granulocytes are also found in these organs, they remain in the background.

2. Chronic “Primary” Erythroblastosis

In 1941 Heilmeyer and Schoner2 described a chronic “primary” erythroblastosis (“erythremoid myelosis”). The erythroblasts in the peripheral blood of their patient numbered 122 per 100 white cells. In the bone marrow smears, more than 3,000 nucleated red cells were counted against 100 cells of the granulopoietic system. There was marked erythropoietic metaplasia in both the liver and the spleen. Several immature granulocytes were also noted in the peripheral blood; myeloblasts, however, appeared only during the terminal phase. Few cases of this chronic form of “primary” erythroblastosis have been described in the literature.

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3. **Erythremia**

The above syndrome\(^2\) must not be mistaken for erythremia (Wintrobe)\(^4\) or polycythemia vera. This chronic illness which is characterized by an abnormally high peripheral red cell count and hemoglobin shows, in addition, hyperplasia of the erythroid series in the bone marrow. This hyperplasia is not nearly so marked as the proliferation described under “primary” erythroblastosis. Moreover, in polycythemia there is a very active and often hyperplastic granulocytic system, whereas in “primary” erythroblastosis the granulocytic system is apparently overgrown. Erythroblasts may be found in the peripheral blood in polycythemia vera, but they are rarely present in overwhelming numbers. Yet Dustin\(^5\) described a patient with a polycythemia, with 80 erythroblasts against 100 leukocytes and Stone and Woodman\(^6\) described a patient with a polycythemia vera, who at times showed over 80,000 erythroblasts per mm.\(^3\)

Transitional forms of erythremia and myeloid leukemia have been repeatedly described, either with or without previous roentgen- or phenylhydrazine-therapy (Wintrobe). There seems to be a close relationship between erythremia and myeloid leukemia (Minot and Buckman;\(^7\) and MacAlpnam\(^8\)).

4. **Erythroblastosis in Myeloid Leukemia**

Erythroblasts are frequently seen in the peripheral blood of patients with myeloid leukemia. MacMichael and MacNee,\(^9\) however, seldom found that they constituted more than 5 per cent of the number of granulocytes in chronic myeloid leukemia. In 74 cases of acute myelosis, Moeschlin\(^10\) found a maximum of 30 per cent of nucleated red cells per 100 white cells in one case. Their number therefore is usually not great in proportion to the white cells.

5. **Erythroleukemia**

Isaës\(^11\) in 1929 described a patient with 79,000 to 220,000 erythroblasts per mm.\(^3\); in addition numerous immature granulocytes were seen in the peripheral blood. Nucleated red cells in the bone marrow amounted to 67 per cent of the total number. Duesberg\(^12\) also described such a combination of erythroid hyperplasia and increase of the myeloblasts in the bone marrow, together with many erythroblasts and myeloblasts in the peripheral blood. This combination has since been called erythroleukemia, indicating myelocytic leukemia combined with a hyperplasia of the erythropoietic system in the bone marrow and peripheral erythroblastosis.

6. **Chronic Erythroblastosis with Splenomegaly as Described by Weil**

Weil\(^13\) as well as several others, especially French authors (Demole and Guye,\(^14\) May,\(^15\) Arnet,\(^16\) Waitz and Waiter\(^17\)), described a chronic erythroblastosis in adults with a pronounced enlargement of the spleen. Marrow puncture revealed a normal picture initially but at a later stage, various abnormalities could be seen. In the spleen an infiltration of erythroblasts was found. Quite often megakaryocytes, sometimes in great numbers, were discovered in the spleen and liver. Weil considered this syndrome to be an inflammatory reaction confined to the liver and spleen, and sparing the bone marrow. Etiologically tuberculosis, hies,
etc., seemed to play a part. Later Weil described the same syndrome, but without erythroblastosis and called it crypto-erythroblastosis. His diagnoses were based on examination of smears obtained by the punctures of the spleen and liver.

7. Leuko-erythroblastosis

Vaughan described patients with anemia in which erythroblasts occurred in the peripheral blood accompanied by immature white cells. This syndrome was called leuko-erythroblastic anemia. Later it was discovered that anemia was not always present, the number of erythrocytes being normal, or even increased to polycythemic levels. Therefore, the term, leuko-erythroblastosis (Wintrobe) is preferable. Enormous splenomegaly was usually conspicuous. Bone marrow puncture revealed a great variety of pictures. In some, no marrow could be aspirated at all. Bone marrow trephination showed a large part of the medullary cavity to be obliterated by osteofibrosis and sometimes by ossification. In other places the marrow was often hyperplastic or normal (MacMichael and MacNee). For this reason this syndrome has also been called myelosclerosis. In the spleen and liver marked myeloid metaplasia was found.

A similar leuko-erythroblastosis may be seen in metastases of tumors, to the bone marrow, and in disseminated osteal processes (e.g., primary tumors, marble bone disease, myelomatosis, etc.). Bone marrow puncture may provide the correct diagnosis in each instance.

8. "Agnogenic" Myeloid Metaplasia of the Spleen

In the American literature during the past few years, a syndrome has been described under the designation of "agnogenic" myeloid metaplasia of the spleen. This same syndrome had been known for a long time under other names. In the greatly enlarged spleen, a marked metaplasia of all blood cells and their earlier stages is found. The bone marrow may show a normal picture, hyperplasia, or fibrosis. In the circulating blood immature elements are found both of erythropoietic and granulopoietic origin. Some of these cases resemble the leuko-erythroblastosis described by Vaughan and Hickling; others resemble the chronic erythroblastosis of Weil. Heller supposed this syndrome to be an aleukemic myelosis (cf. Hickling). Wintrobe like Vaughan suggests that the function of the bone marrow in these cases is insufficient owing to a deficiency of an unknown factor. This results in a compensatory metaplasia. In the splenic metaplasia, an increase of megakaryocytes is often an important feature.

9. Erythroblastosis Fetalis

This type of erythroblastosis occurs only in the newborn.

10. Cooley's Anemia

In children of Mediterranean origin a hereditary blood dyscrasia occurs, called Cooley's anemia or Thalassemia major. Here the occurrence of erythroblasts in the blood picture is characteristic. A similar though milder syndrome has been discovered in older children and adults; in these cases, nucleated red cells are not customarily found.
11. Erythroblastosis as a Symptom in some Other Diseases

Finally erythroblasts may be found as a "symptomatic" phenomenon in the circulating blood under various sets of circumstances, since acute bleeding often leads to the frequency of nucleated red cells. In patients with either congenital or acquired hemolytic anemia, the number of erythroblasts may be several times greater than the number of white cells in the peripheral blood. Similarly, we may see it in occasional cases of pernicious anemia. Well known also is the erythroblastosis of sprue (tropical diarrhea) as described by van Buchem. In black-water fever ("hemolytic" malaria) many erythroblasts may occur in the blood during the crises. It is generally known that after splenectomy, temporary erythroblastosis may occur. Groen and Godfried described a distinct erythroblastosis in patients with decompenated heart disease as a sign of unfavorable prognosis.

The present case, in which there was first erythroblastosis, later to be followed by the typical features of acute leukemia is now presented.

Case Report

In September 1945, a 29 year old office clerk began to complain of feeling tired. On admission to his local hospital on October 16, 1945, the patient appeared jaundiced and pale. No abdominal viscera could be palpated and the lymph nodes were not enlarged. The remainder of the physical examination was completely negative. The temperature was sub-febrile to febrile. Urobilin but no bilirubin was found in the urine. The bilirubin content of the blood was normal, being 0.4 mg. per cent. Gastric analysis showed achlorhydria, refractory to histamine.

The blood picture was as follows: Hgb. 43 per cent; RBC 2.3M; WBC 7,700. Differential count: eosinophiles 2; basophiles 0; immature granulocytes 5; "stab" forms 5; segmented forms 37; lymphocytes 49; monocytes 2.

For every 100 white cells, there were 73 nucleated erythrocytes (erythroblasts), many of them small, relatively mature forms. The number of thrombocytes was reduced: 30,000 per mm. The red blood cells showed anisoctyosis, poikilocytosis and polychromatophilia. The fragility test showed beginning hemolysis at 0.48 per cent and complete hemolysis at 0.40 per cent of salt solution. Later on it was found that the bleeding and coagulation times were normal, while the Rumpel-Leede phenomenon could not be elicited. Blood serology was negative. The bone marrow puncture on the day after admission revealed marked hyperplasia of the erythropoietic system. Unfortunately a marrow differential was not performed at this time.

In spite of blood transfusions the patient's course was downhill. Details of the blood picture are presented in chart 1. On November 3, 1945, splenectomy was performed; the spleen weighed 340 Gm. Microscopic examination revealed marked myeloid metaplasia.

After removal of the spleen, the number of leukocytes and erythrocytes increased somewhat. Generally speaking, however, there were no changes of importance.

On January 15, 1946 the patient was admitted to the Medical Clinic at Utrecht. Physical examination showed a pale, well nourished man. His temperature was 38.4 C. Some lymph glands, the size of a hazel nut, were palpable in groins, armpits and neck. The liver was palpable two fingerbreadths beneath the right costal margin. The urine contained much urobilin, but no albumin, and no Bence-Jones protein. The sedimentation rate was 126 mm. in one hour (Westergren). The bilirubin content of the blood serum was not increased: 0.7 mg. per cent. The calcium content was 11.9 mg. per cent, inorganic phosphate 4.5 mg. per cent. "Alkaline" phosphatase 2.8 u. The iron content of the serum was 75 (before breakfast).

Blood picture: Hgb. 42 per cent; RBC 1,330,000; average diameter of red cells 8.1 μ.
ERYTHROBLASTOSIS AND LEUKEMIA

Reticulocytes 20 to 60 per cent; leukocytes 8,200; erythroblasts 158,000 per mm.3. Differential count: eosinophiles 2; basophiles 0; myeloblasts 5; "stab" forms 12; segmented forms 38; lymphocytes 30; pathologic lymphocytes 8; monocytes 4; plasma cells 1. Differential count of the nucleated red cells in the blood showed the following: basophilic erythroblasts 6, polychromatophilic erythroblasts 466, orthochromatic erythroblasts 1,466, forming a total of about 1,900 erythroblasts to every 100 leukocytes (see fig. 1). Most of the erythroblasts were small normoblasts with pyknotic nuclei. Several showed a so-called arrested mitosis, i.e., smaller and larger pieces of nuclei in a rosette of clover-leaf forms (fig. 1). At times, binucleated cells were seen. There was only a small number of large erythroblasts, mostly polychromatophilic, but in a few instances basophilic. The reader is referred to chart 2 for the further course of the blood picture.

No occult blood was found in the stools. On the day of admission, bone marrow puncture was done. In the aspirate a marked hyperplasia of the erythropoietic system was found, amounting to more than 67 per cent of the nucleated cells (fig. 2). A "shift to the left" of about 10 per cent of myeloblasts among the granulopoietic cells was very conspicuous. Although the marrow was richly cellular, the number of megakaryocytes was markedly reduced. While orthochromatotic forms dominated the erythroblasts in the peripheral blood, the basophilic and polychromatophilic elements with round nuclei prevailed in the bone marrow. Macroblasts were rare. Most of the nucleated red cells were middle sized or small. Some of the myeloblasts in the peripheral blood showed Auer bodies in their cytoplasm (fig. 3). X-ray examination revealed no abnormalities in the skeleton (cranium, thorax, pelvis), heart and lungs.
Fig. 1.—Smear of the peripheral blood (1-15-1946) showing the variation in appearance of the erythroblasts. Most nucleoli are pyknotic and many of them have a rosette-form or are "fragmentated."

Fig. 2.—Smear of the bone marrow (1-15-1946) showing hyperplasia of the erythropoietic system, the erythroblasts mostly showing round nuclei as contrasted with their appearance in the peripheral blood. In addition some myeloblasts are seen.

During his hospital stay, the patient ran an irregular but unremitting fever. Repeated infections of the skin with abscess formation in the subcutaneous tissues occurred; these responded satisfactorily to penicillin. The anemia responded neither to liver extract, fer-
4.-Smear of peripheral blood (10-8-1946); the erythroblasts have practically disappeared and we now see mainly an enormous increase of myeloblasts.

During the following month the number of erythroblasts in the peripheral blood re-
remained high, ranging between 10,000 to 150,000 per mm$^3$ while the number of immature granulocytes remained low: between 0 and 10 per cent (chart 2).

In the bone marrow, however, the number of myeloblasts increased slowly. On May 23, 1946, the number of erythroblasts in the bone marrow had fallen to about 20 per cent of the nucleated cells, while the granulocytes rose to about 67 per cent. In September 1946 this proportion was 17 and 80 per cent respectively. The number of myeloblasts rose to 37 per cent of all the granulocytic series. During this period the number of immature granulocytes in the circulating blood was still more or less the same: 0 to 10 per cent of all white cells.

At the beginning of October 1946 a sudden change in the blood picture occurred. The leukocyte count rose to 100,000 per mm$^3$ with a considerable shift to the left. Differential count at this time revealed 58 per cent myeloblasts. The number of erythroblasts now amounted only to 12,000 per mm$^3$. The number of myeloblasts in the peripheral blood then rose to over 90 per cent, while the erythroblasts practically disappeared from the circulating blood (fig. 4). In the bone marrow the morbid growth of the myeloblasts now superseded all other cells. This myeloblastosis continued until death, which occurred on October 20, 1946, more than a year after the onset of the disease.

Two lymph node biopsies were performed during the patient’s life. The reports of the microscopic examination are given under the autopsy report.

**Autopsy Report**

We shall first give a short description of the microscopic examination of the extirpated spleen and the two lymph node biopsies.
November 7, 1945, spleen: weight 340 Gm. The follicles are just visible on section. The pulp is very rich in cells. The greater part of the cells are myeloid elements, among which are found myelocytes of various types, the eosinophilic granulocytes being particularly easy to recognize. There are also a great number of young cells of the erythroblast series. Often, the nuclei of the cells consist of two oval parts connected by a long and very thin thread of chromatin.

March 21, 1946, lymph node (biopsy). The microscopic picture shows that the architecture of the lymph gland has been replaced by polymorphous granulation tissue with a great many eosinophiles and some giant cells of the Sternberg type. This picture is suggestive of Hodgkin’s disease.

June 4, 1946, lymph node (biopsy). The architecture of the lymph gland has been replaced by a more monomorphous granulation tissue with a great many eosinophiles and sporadic giant cells. This is an atypical picture upon which no diagnosis can be made.

October 21, 1946, autopsy, 44 hours postmortem. Only the most important items are given.

Gross Findings: In the thorax and abdomen are found many fairly enlarged lymph glands. The hilus glands of the lungs contain old tuberculous lesions. There is a fibrinous pleurisy over the lower lobe of the right lung. Both lower lobes are firm and on section show slight pneumatic changes. The liver is enlarged (3,000 Gm.). On section the bone marrow of the vertebrae has a greyish-pink color.

Microscopic: In all sections, many white blood cells of the myeloblast type are found in the blood vessels. This same type of cell is seen outside the blood vessels in the tissues of many organs.

Lymph Nodes: In the hilar nodes of the lung there are old and recent tuberculous changes. The normal architecture of the lymph nodes lying in the neck, lung hilus and abdomen is for the greater part lost. Remnants of follicles are found in a few places. The nodes are strewn with myeloblasts. Polymorphonuclear erythroblasts are present but are very small in number.

Liver: The portal areas contain foci of myeloid cells, which are not very clearcut. Among these cells are found some eosinophiles. Between the hepatic cells accumulations of myeloblasts are found. In the perportal connective tissue, in the liver cells and in the Kupffer cells there is considerable iron pigment.

Vertebræ: The bone trabeculae are thin and show evidence of resorption. Instead of the normal architecture of the marrow are seen myeloblasts, many mitotic figures and some giant cells.

Kidney: In the connective tissue of the cortex, there are several myeloid foci. These consist of myeloblasts, some polymorphonuclear erythroblasts and eosinophiles.

Lungs: There is a fibrinous pleurisy, a fibrinous, hemorrhagic pneumonia, myeloid infiltration and hemorrhages in the interstitial tissues.

Heart: No special abnormalities.

Surveying the changes in the organs which occurred in the course of the illness, we may summarize these as follows:

November 7, 1945, myeloid and erythroblastic proliferation in the spleen.

March 21, 1946, granulatation tissue in a cervical gland, resembling that found in Hodgkin’s disease.

June 4, 1946, histologic picture of another lymph node biopsy resembling Hodgkin’s disease far less, but not characteristic of leukemia either. These changes in the lymph glands might also have resulted from the inflammatory processes in the mouth and nose (see below).


Diagnosis: from the very onset, the erythroblastosis dominated the clinical picture in this patient. For months the number of erythroblasts fluctuated be-
tween 10,000 and 150,000 per mm.² During this period the immature granulocytes in the peripheral blood amounted to only 0 to 10 per cent of the leukocytes. In the bone marrow the erythroid-myeloid ratio was inverted in the beginning (January, 1946), viz., 2½:1. On account of the great hyperplasia and anaplasia, i.e., incapability of erythroblasts in the bone marrow to attain a mature structure and function, and of the dysplasia, i.e., the great number of pathologic, atypical erythroblasts in the circulating blood, the possibility of a “primary” erythroblastosis of Di Guglielmo had to be taken into account. In this syndrome, immature granulocytes apparently occur in the blood.

However, the increased number of myeloblasts in the marrow, already present at the time of our first puncture (January 15, 1946) was an indication that an abnormality of the leukopoietic system should also be considered. After the number of myeloblasts increased, first in the bone marrow and later in the peripheral blood, it became clear that a myeloid leukemia existed in addition to the hyperplasia and dysplasia of erythropoiesis. As already mentioned in the introduction, this combination has been described as erythro-leukemia by Moeschlin² and Duesberg.¹ The myeloblastic crisis occurring shortly before death pointed to the ultimately dominating role of the granulopoietic system in this disease.

**Discussion**

Presumably our patient would have died in the initial erythroblastic stage if he had not received so many transfusions and so much penicillin. In that case the diagnosis would probably have been “primary” subacute erythroblastosis, as described by Heilmeyer and Schoner⁶ and by Di Guglielmo.¹

The present case history illustrates in our opinion the close relationship that exists between the pathologic proliferations of the erythropoietic and the granulopoietic systems and possibly between the “primary” erythroblastoses and myeloid leukemia.

The impression prevailed that something in the “red” as well as in the “white” system of our patient had become abnormal from the beginning of the illness. It is also possible, however, that this case demonstrated the deterioration and proliferation of a primitive mesenchymal cell with multipotential hematopoietic tendencies. It may be imagined that at first immature and often atypical erythroblasts were formed, which were functionally inferior and that later myeloblasts, which were also functionally inferior, dominated the picture.

In the course of the illness, severe infections occurred repeatedly. These did not seem to be of etiologic importance in this patient, as they were not present during the first hospitalization, although the blood picture even then showed a serious erythroblastosis. These inflammatory processes probably occurred as a result of diminished defense mechanisms, possibly connected with the shortage of mature granulocytes.

Many blood transfusions together with the repeated administration of penicillin prolonged the patient’s life. Consequently the proliferating “white” system received enough time to supersede eventually the “red” cell system and the patient died, presenting the typical picture of myeloblastic leukemia.

Various associated hematologic syndromes are now seen more frequently in
the leukemic patient than was the case previously. The prolongation of life in these patients by transfusions and antibiotics may well account for this. Thus various syndromes, heretofore described under different designations, may prove to be variations of one and the same disease. Dameshek\textsuperscript{20} has dilated on this point in his editorial entitled "Some speculations on the myeloproliferative syndromes." It remains to be seen, however, if one should go as far as Heller\textsuperscript{26} who regards practically all diseases with myeloid metaplasia of the spleen as variants of myeloid leukemia.

In the introduction we have discussed the most important diseases in which nucleated red cells occur in the blood. Many hematologists assume that these young red cells originate from foci lying outside the bone marrow (Rohr\textsuperscript{23}). Others believe that in the case of a morbid growth of the red system, abnormal juvenile red cells may gain access to the peripheral blood directly from the bone marrow.

Little attention has been paid to the possibility that an altered function of the spleen may contribute to the occurrence of juvenile red cells in the peripheral blood. We know that juvenile red cells are often found in the blood after splenectomy. With some diseases, e.g., blackwater fever, many erythroblasts appear in the blood during which the spleen swells greatly. Increased hemolysis alone cannot be the cause of this erythroblastosis, as we may find only few erythroblasts or none at all in the blood after a still greater destruction of the blood.

From the beginning of the patient's illness, a well defined anemia was present which threatened the patient's life. Hemolysis, which might have explained the anemia, seemed improbable in view of the normal bilirubin content of the serum; nor was there evidence of blood loss. Hyperplasia of the "red" system was present in the bone marrow at the same time. This hyperplasia, however, was of a pathologic nature. It was anaplastic, there being a relatively marked decrease of orthochromatic normoblasts. This pathologic anaplasia and the formation of abnormal erythroblasts which appeared in the blood pointed to a deterioration of the erythropoietic system. Consequently too few erythroblasts which were functionally normal were apparently produced and an anemia resulted.

Once more it seems important to point out the sometimes deceptive similarity of the histologic picture as found in lymph node biopsies from cases of leukemia and Hodgkin's disease. Downey\textsuperscript{44} (cf. also Watson,\textsuperscript{25} Barth,\textsuperscript{26} Calender\textsuperscript{27}) states in his handbook that the presence of megakaryocytes in lymph glands and spleen in cases of myeloid leukemia may be very suggestive of Hodgkin's disease. In our own biopsies the combination of a considerable eosinophilia together with giant cells made the picture hardly distinguishable from Hodgkin's disease. The number of eosinophiles was greater than that usually found in myeloid leukemias, and also much greater than was found in the bone marrow at that time. If we regard the lymph node changes as a part of this erythro-leukemia (megakaryocytes are found among the giant cells), a differentiation in a far more eosinophilic direction was found in the lymph nodes than in the sternum. It is not impossible, however, that allergic or inflammatory processes may have influenced the microscopic picture of these cervical lymph nodes. In the literature pathologic changes in regional lymph nodes in cases of inflammatory processes are

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mentioned which cannot be distinguished from Hodgkin’s disease (Abrikossof, Terplan and Skworzoff and Ussanowa).

SUMMARY

The authors report the case of a man, 29 years old, who presented initially a marked erythroblastosis (10,000 to 150,000 erythroblasts per mm.) in the peripheral blood. Originally, a great hyperplasia of the red system in the bone marrow existed. Gradually this morbid growth of the “red” system was superseded by a proliferation of myeloblasts.

After an illness of about one year’s duration the patient died in a myeloblastic “crisis.”

It is pointed out that owing to prolongation of life in this case through repeated blood transfusions and penicillin, the opportunity was presented to observe different hematologic syndromes in the same patient. With the common use of potent therapeutic procedures this situation is now increasingly present. It may lead to the ultimate recognition that different hematologic syndromes are in reality different manifestations of the same disease.

The various diseases in which an erythroblastosis may occur are discussed.

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